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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,792	03/28/2005	Kenji Hashimoto	2004 2053A	3058

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EXAMINER	
KINGAN, TIMOTHY G	
ART UNIT	PAPER NUMBER
1797	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,792	HASHIMOTO ET AL.	
	Examiner	Art Unit	
	TIMOTHY G. KINGAN	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,16 and 18-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,16 and 18-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/29/2004, 03/28/2005 and 07/03/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 10, applicant recites "selecting patients with schizophrenia for whom the D-serine therapy is effective." Yet applicant has not defined any criteria by which this "effectiveness" is judged.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1, 10-12, 19-21, 23 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by G. Tsai et al., Biological Psychiatry 44:1081-1089, 1998 (herein after Tsai).

For Claim 1, Tsai teaches the step of measuring concentrations of D- and L-serine in serum of patients fulfilling the diagnosis of schizophrenia (p. 1082, col 2, ¶ 5 and p. 1083, col 2, ¶ 2).

For Claim 10, Tsai teaches that levels of D-serine in the treatment group are positively correlated with measures of cognitive improvement (patients selected with schizophrenia for whom D-serine therapy is effective) (p. 1084, col 1, ¶ 4 and Table 4).

For Claims 11-12 and 19-21 Tsai teaches the steps of labeling amino acids with an amino acid labeling reagent (contacting an amino acid labeling reagent with a biological sample) comprising o-phthaldialdehyde (amino acid fluorescence-labeling reagent) by precolumn derivatization (p. 1083, col 2, ¶ 2) and fractionation of derivatized amino acids, including D-serine and L-serine (separating labeled D- and L-serine), in a reverse phase (high performance) column by liquid chromatography with quantitation by fluorescence detection (optical resolution) (p. 1083, col 2, ¶ 2).

For Claims 23-24, Tsai teaches an amino acid labeling reagent comprising *o*-phthaldialdehyde (amino acid labeling reagent) which reacts to create fluorescent derivatives (p. 1083, col 2, ¶ 2) (fluorescent-labeling reagent).

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 2-4, 6-9, 13, 16, 18 and 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsai.

For Claim 2, Tsai does not teach the step of measuring an index of D-serine in samples from healthy individuals and those with diagnosis of schizophrenia. Tsai does teach measuring serum levels of D-serine in two groups of affected individuals (p. 1086, Table 3), but not in healthy controls. It would have been obvious to one of ordinary skill in the art at the time of invention to measure D-serine in such group in order to provide support for the hypothesis of a link between altered activity of the NMDA-type glutamate receptor and schizophrenia, and a partial basis for this link in activity of D-serine at the glycine modulatory site of the receptor.

For Claim 3, Tsai is silent on use of an index comprising comparison with average - standard deviation of the value in healthy individuals. Such comparison based on a statistical distribution of values is known in the art and would have been obvious to one of ordinary skill in the art, and it would have been desirable to use such comparison in order to provide an index the significance of which could be most easily evaluated by researchers and clinicians.

For Claim 4, Tsai is silent on an index in which comparison is to average + standard deviation of a value for individuals with schizophrenia. Such comparison would have been obvious to one of ordinary skill in the art in order to provide for an indication that a value for an affected individual falls within a range of certain confidence limits for affected individuals. Further, such comparison would be desirable in making provision for dividing affected individuals into treatment groups.

For Claims 6-8, Tsai is silent on use of an index comparing D-serine to total serine. It would have been obvious to one of ordinary skill in the art at the time of invention to use such index in order to provide for uncovering the possibility that skewed values of D-serine in affected individuals (either low or high) are attributable to skewed values of total serine which would affect absolute levels of D-serine through the racemase. Further, forming such ratio for evaluation would normalize the effects of changes in total serine, and the inclusion of the standard deviation in evaluating the ratio would be obvious to one of ordinary skill in the art in order to provide for readily recognized statistical significance.

For Claim 9, Tsai is silent on evaluating an index based on its value being lower than average + standard deviation. Such comparison would have been obvious to one of ordinary skill in the art in order to provide for an indication that a value for an affected individual falls within a range of certain confidence limits for affected individuals.

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For Claims 13, 16 and 18, Tsai is silent on separating and quantifying labeled serine by high-performance liquid chromatography before the step of separating labeled D- and L-serine. It would have been obvious to one of ordinary skill in the art at the time of invention to use such separation and quantitation in order to prescreen samples for total serine, in a system with fewer analytical demands than those that may be required for chiral separations, for the purpose of grouping or prioritizing samples on the basis of total serine for subsequent analysis of enantiomers. Further, it would have been obvious to one of ordinary skill in the art that such separation would be done by chromatography in a system similar to that used for D- and L-serine comprising a reverse phase column

that fractionates on the basis of hydrophobic character of the derivatives (high performance) but does not separate derivatized D- and L-serine.

For Claims 26-27, Tsai does not teach a method of examining schizophrenia using D- and L-serine measurements. Tsai does teach the step of measuring concentrations of D- and L-serine in serum of patients fulfilling the diagnosis of schizophrenia (p. 1082, col 2, ¶ 5 and p. 1083, col 2, ¶ 2). It would have been obvious to one of ordinary skill in the art, from these teachings of Tsai, to use such measurements of D- and L-serine or D-serine alone, either increasing or decreasing with respect to those of a control group, as an index of examining schizophrenia.

6. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tsai as applied to claim 1 above, and further in view of S.H. Snyder and P.M. Kim, Neurochemical Research 25(5): 553-560, 2000 (herein after Snyder).

For Claim 5, Tsai is silent on use of an index the extent to which L-serine is higher than in a group of healthy individuals. Tsai does teach measuring L-serine in the two groups of affected individuals (p. 1086, Table 3). Tsai also teaches that D-serine can be converted to L-serine by a racemase (p 1086, col 1 ¶ to col 2 ¶ 1). Further, Snyder teaches that D-serine is present in high concentrations in glial cells in the forebrain with a distribution closely resembling that of NMDA receptors (p. 554, col 2, ¶ 2, and the whole document), and that the racemase which interconverts D- and L-serine labels the same astrocytes containing D-serine (p. 557, col 1, ¶ 5). From these considerations on the source of D-serine and the distribution of that source with respect

to neurons containing the proposed affected receptors, in would have been obvious to one of ordinary skill in the art to use an index comprising the level of L-serine in order to test the possibility that symptoms in individuals with schizophrenia could be partially explained by a level, activity or distribution of a racemase favoring increased formation of L-serine while lowering D-serine needed at the glycine-modulatory site of the NMDA receptor.

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7. Claims 22 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsai as applied to claims 21 and 24, respectively, above, and further in view of H. Watanabe and E. Kawamura, Japanese Patent Application Publication 61-080051 (herein after Watanabe).

For Claims 22, Tsai is silent on the step of using the reagent 4-fluoro-7-nitro-2,1,3-benzoxadiazole as fluorescence-labeling reagent. Watanabe teaches the step of using 7-fluoro-4-nitrobenzo-2-oxa-3-diazol (alternate nomenclature for the compound of the instant claim) as amino acid labeling reagent for fluorescence detection (abstract). One of ordinary skill in the art at the time of invention would have found obvious to use the reagent of Watanabe in the method of Tsai for labeling amino acids in order to provide a reactive reagent with excitation and emission spectra adequate for optical resolution.

8. Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tsai in view of S.H. Snyder and P.M. Kim, Neurochemical Research 25(5): 553-560, 2000 (herein after Snyder).

For Claim 28, Tsai is silent on use of an increase in L-serine as an index. Tsai does teach measuring L-serine in two groups of affected individuals (p. 1086, Table 3). Tsai also teaches that D-serine can be converted to L-serine by a racemase (p 1086, col 1 ¶ 3 to col 2 ¶ 1). Further, Snyder teaches that D-serine and the racemase are present in high concentrations in astrocytes with a distribution closely resembling that of NMDA receptors linked with the symptoms of schizophrenia (p. 554, col 2, ¶ 2, and the whole document). From these considerations, in would have been obvious to one of ordinary skill in the art to use an index comprising an increase in the level of L-serine in order to test the possibility that symptoms in affected individuals could be partially explained by the activity of a racemase favoring formation of L-serine while lowering D-serine, the enantiomer shown to be a positive regulator at the glycine modulatory site.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY G. KINGAN whose telephone number is (571)270-3720. The examiner can normally be reached on Monday-Friday, 8:30 A.M. to 5:00 P.M., E.S.T.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on 571 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TGK

/Jill Warden/
Supervisory Patent Examiner, Art Unit 1797

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